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Environmental Factors in Cancer: Trichloroethylene and Related Solvents: Science, Regulation, and Cancer Prevention:

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INTRODUCTION

In this brief White Paper, I present a case study of research and regulation on a solvent to demonstrate how barriers can impede research and regulation. The solvent I describe, TCE, or trichloroethylene, has chemical properties that make it very desirable for industrial uses. However, the chemical turned out to be associated with the occurrence of certain cancers and other diseases in populations of worker who used it or were exposed to it. As health hazard evidence began to accrue, the regulatory agencies did not respond aggressively. This problem expanded as the chemical began to be found in the environment, largely as the result of improper disposal, exposing substantial portions of the public to the same chemical, typically at lower concentrations. Definitive research has been slow to follow, the regulatory response continues to be somewhat cautious and limited, and, still today, various barriers impede research. What is most troubling about this story is that: (1) limited regulatory action has been taken to lower and/or prevent occupational and environmental exposures; (2) the data needed to study and document this problem are not easily accessible to researchers; and (3) the US EPA, which began a thorough reassessment of its regulation of TCE in the mid to late 1990s, still has not taken (appropriate) action to strengthen regulations, to reduce residential and other public exposures by facilitating remediation.

TCE: WHAT IS IT AND HOW IS IT USED?

TCE is a synthetic compound, a chlorinated solvent that first was used as an analgesic and anesthetic beginning around 1900. Then, over the next few decades TCE was used commonly as a commercial dry cleaning agent, in other industries as a solvent and vapor degreasing agent for metals and in a few other applications.1** TCE was popular, in part, because it has very low flammability/exposivity, making the fire risk substantially lower than with many alternative chemicals. By 1960, TCE use dry cleaning was largely replaced by the use of tetrachloroethylene, or FERC. However, TCE is still used today in substantial quantities as an industrial solvent and vapor degreasing agent.

TCE Exposures

While TCE was a desirable chemical to use in industrial settings because of its low flammability, it was far less desirable from a worker health perspective because of its volatility and lipophilic properties, because it can result in exposure through inhalation and skin contact in workers who are not using adequate protection. In addition, because it was often disposed of improperly, being dumped on the ground or in waterways, many underground water sources became contaminated with TCE. Today, TCE is the most frequently detected organic solvent in ground-water supplies, has been found in more than 60% of the 1,428 Superfund sites nationwide, and is estimated to be in as many as 34% of the nation's drinking water supplies. It has been shown that once in the ground water, TCE may evaporate, infiltrating private residences as a gas (i.e., vapor intrusion), creating in inhalation and ingestion risks/1/.

RESEARCH ON THE CARCINOGENICITY OF TCE

There has been much controversy over the possible carcinogenicity of TCE. In the late 1970s, epidemiologic studies of European workers with documented exposures to TCE reported some elevated cancer rates /2-5/, as did US studies of laundry and drycleaners /6-8/, metal workers /9/, and others, some of which were consistent with results of experimental animal studies. During the 1980s and 1990s various regulatory exposure limits were developed (see below) and, while expert panels acknowledged the observed increased incidence of cancers in workers exposed to TCE, they generally felt that the suggestive data were not sufficient to declare TCE a known human carcinogen. For example, in the mid to late 1990s, both the International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP) concluded that TCE is, "probably carcinogenic to humans (Group 2A)" /10/, and "reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals /10,11/. In the mid 1990s, the EPA began a broad reassessment of the health effects to members of the public exposed to TCE. My research group was fortunate to be funded by EPA to conduct a review of the TCE-related cancer epidemiology as part of this reassessment. In 2000, we published our findings, showing probable associations of TCE with kidney cancer, liver cancer and non-Hodgkin lymphoma, and possible associations with other cancers /12/. We, and others, also identified gaps and weaknesses in the published studies, such as lack of precise tools to accurately measure individual exposures, incomplete employment records, inaccuracies in death certificates, lack of available cancer incidence data, and the observation that in almost all of the studies TCE there was simultaneous exposure to a variety of solvents and other potentially hazardous chemicals, making it difficult to determine conclusively which agent was responsible /13,14/.

More recent work has begun to elucidate some of the specific mechanisms of action of TCE and its metabolites, strengthening the case against TCE, such as the observation of an increased rate of mutation in the VHL tumor suppressor gene among TCE exposed individuals /15, 16/ and evidence that TCE can act as a complete kidney carcinogen /17,18/.

BARRIERS TO RESEARCH

Occupational Populations

One of the research challenges in trying to advance our knowledge on the carcinogenicity of TCE is the identification of situations that directly address controversial or unresolved issues. Some colleagues at a state health department have identified such a situation in which the only solvent to which workers in a specific facility were exposed was TCE, overcoming the common problem of simultaneous exposure to multiple solvents, noted above. The cohort had been followed by the company for many years, but through various bankruptcy and related proceedings, the worker data now reside with a holding company and also with a subsidiary of the company that bought out the original company, under which the workers had been exposed. Despite repeated requests, the health department staff has been unable to obtain complete worker lists, employment records and job titles. Similar but more limited data exist with the US Internal Revenue Service (yearly data on place of employment), but the health department does not have the legal authority to obtain these records. The health department staff has spent several years trying to obtain these data, have conducted preliminary studies with data they did obtain, but cannot conduct a sufficiently reliable study without the more complete data being harbored by these entities. For example, with a complete employee list (ideally, with social security number), and years of employment, they could request both cancer incidence data from state registries and mortality data from the National Death Index. With employment history and job titles for all employees, one could make some reasonable, albeit, approximate, assumptions about exposures (e.g., drinking water ingestion, use of TCE in degreasing activities), and assess incidence of specific cancers versus years worked and actions performed, adjusted for sociodemographic and other confounding variables, and a similar mortality analysis, looking at several individual causes of death, including specific cancers. While not as rigorous as direct exposure data, such a study would focus more directly on TCE only, than has been possible in most previous occupational studies. Currently, estimates of exposures for studies of these workers, using traditional approaches, would have serious limitations, compromising possible interpretation. It is likely that one of the main issues preventing release of the employment data is concern about confidentiality of data with personal identifiers. However, health department staff routinely manages such data and have the authority to prevent their release, when appropriate. Another concern may be that the use and refinement of these data may lead to work products that could be used in legal proceedings (on either side). While this concern is valid, it would be in the interest of public health and disease prevention that a mechanism be devised to facilitate the science study in spite of these concerns. The goal of the research would be to evaluate and report only aggregate data, but individual data records are needed to facilitate this research. The failure to provide relevant and complete data is a major barrier to our possible understanding of the carcinogenicity of TCE.

Population-Based Surveillance

A second approach for conducting research to better understand the carcinogenicity of TCE is the use of routinely collected cancer data to examine cancer rates in the vicinity of TCE use, release and contamination. New York State, in conjunction with the Agency for Toxic

Substances and Disease Registry (ATSDR), undertook such a study in Endicott, NY, an area with substantial vapor intrusion from TCE and PERC /19/. They found statistically significant elevations of kidney and testicular cancer (SIRs of 1.8 and 2.9, respectively) as well as elevated rates of lung and esophageal cancers, all of which have been suggested by previous studies to be associated with TCE exposure. New York State is using these results to help develop exposure remediation programs. This research approach was successful and led to exposure reductions and likely disease prevention. To explore the application of this approach elsewhere, several years ago I began requesting cancer incidence data from two states (and discussed a request informally with a third), including the date of death, location of the decedents' residence at the time of death (e.g., latitude, longitude) and typical sociodemographic risk factors routinely reported on the death certificate. Because this is a fairly common approach to research, both states initially agreed to provide the data as long as I provided the necessary assurances of protection of confidentiality and compliance with federal regulations (e.g., HIPAA) through each state's Institutional Review Board. I did so, as academics routinely do for any research involving human subjects' data. One state then provided the data while the second state refused to, without explicit specification of why the request was refused or recommendations for how to address their unstated concerns. The third state is bound by state law not to release residence information to researchers. This raises three concerns. First, there are different rules and processes for requesting the same type of data from different states, making the data request process extremely cumbersome for those requesting data from several states, which may be necessary to provide regional or national assessments. Second, some states do not feel obligated to make these data available to qualified researchers, even when all the typical approvals and assurances have been provided, and even though many such health departments may not have adequate resources and/or staff to conduct the wide range and large number of studies that could help identify cancer risk factors and suggest ways to prevent cancer. Third, there is no independent oversight of the health departments data release policies and procedures, nor their implementation, to prevent or rectify arbitrary decisions to withhold relevant data. Again, this is a major barrier to research. This example suggests the need for a process to facilitate release of these data for research while protecting subject confidentiality and, more generally, to facilitate broad-based research of this type that could be conducted regionally or nationally, and lead to a better understanding of specific environmental and occupational risks.

Regulatory Impediments

In light of the widespread exposures described above, and the research findings viewed as at least suggestive of TCE's carcinogenicity, it is disappointing that regulatory process is lagging so far behind the science. One of the basic tenets of good public health practice is that to avoid death and disease one should prevent hazardous exposures, where possible, and when in doubt, err on the side of caution. Currently, there are regulations in place with respect to TCE exposure. But the OSHA rule dates back to 1993, the EPA rule to 1985.1 Much new science has been conducted since then, most of which suggests greater risk from exposure to TCE than did the previous studies. EPA did initiate a process to review this issue, their Reassessment, which produced a report and series of papers published in a peer-reviewed journal, and these materials were reviewed by their Scientific Advisory Board. In

spite of this information suggesting a greater hazard than had been acknowledged previously, rather than promulgating more stringent exposure regulations, they requested a review by the National Academy of Sciences. That report was completed six years later, in 2006, and supported the basic findings of the EFA's Reassessment. 18 Still, as far as I know, EPA has not undertaken any formal reconsideration of their exposure regulations. I do not know why there has been so much research activity and so little regulation action on this issue, but during this time we have learned of many more people being exposed to TCE throughout the US. These exposed individuals are being afforded only limited guidance and assistance. I believe more aggressive action is required, setting more stringent exposure regulations, providing more guidance to individuals for how to reduce residential and occupational TCE exposure, and even direct assistance in reducing these exposures.

SUMMARY

In summary, I have used the case of TCE exposure as an example of: (1) The importance of population-based research to identify and characterize possible environmental risk factors for cancer, and the need for a greater emphasis and proportional increase in public funding of research on prevention as compared to treatment. We need to understand these risks better, and use this information to drive effective public health prevention actions. (2) The imposition of strong restrictions on requests by bona fide researchers for access to data as a barrier to research that could be used to help resolve some of the most controversial issues in TCE epidemiology, in particular, and environmental risks in general, especially access to individual level data including data of event and location of residence. Researchers need ready access these data to more accurately characterize environmental exposures, diseases and their possible associations, and to help develop more effective public health preventive actions, although they should also protect confidentiality. (3) The need for more accurate and comprehensive biomarkers of exposure and disease to better assess possible associations between environmental and occupational exposures and disease; (4) The role of non-scientific concerns in limiting regulatory and advisory agencies in the reevaluation of their positions relative to preventing or lowering allowable exposures to TCE, in light of the growing body of evidence on the possible carcinogenicity of a compound still widely in use, to which many workers, and substantial segments of the general public, are exposed.

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